Prediction of Dissolution of Carbamazepine- Fumaric Acid Co- crystal Form B Polymorph in Ethanolic Solution Through Molecular Modelling Approach

Nur Hafizatul Sahera Binti Mohd Zailani, Nornizar Anuar, Umi Rafiah Shukri, and Nik Salwani Md. Azmi

Faculty of Chemical Engineering, Universiti Teknologi Mara

A B S T R A C T

The main objectives of this study are to predict the dissolution of carbamazepine- fumaric acid (CBZ-FUM) Form B polymorph in ethanolic solution by using molecular modelling approach and to establish the interaction of ethanol molecule with co- crystal carbamazepine- fumaric acid (CBZ- FUM). In order to achieve the objectives of the research, the simulation was carried out by using Material Studio (MS) 4.4 software. The dissolution behavior of CBZ- FUM in ethanol solvent was simulated by molecular dynamic (MD) simulation. MD simulations were carried out at 571 ºC and 788 ºC in the NVT ensemble with simulation time of 5 ps and time step 0.1 fs, using the Berendsen thermostat. The predicted morphology has a good agreement to the experimental morphology of CBZ- FUM with 0.0020% deviation of lattice energy value between the predicted and the experimental lattice energy. For this work, the results show that the dissolution favours to occur first at the corners and edges of the crystal morphology followed by the flat surfaces of the crystal. Facet (1 1 -2) molecules located at the corner edges leave the crystal surface first into ethanol solvent phase followed by facet (1 0 -2) and lastly facet (0 1 2), and this result signifies the favourable interactions between the morphology of the crystal and the solvent is the major contributor to the dissolution process. The dissolution result also supported by coefficient diffusion and surface energy result calculated.

Keywords:
Carbamazepine- Fumaric Acid, Co-crystal, Morphology, Solvent, Dissolution, Dynamic Modelling

1. INTRODUCTION

Solubility is a crucial property of drugs as they it must first dissolved so before reach the site of action by absorption mechanism through membranes. Drug solubility is one of the most crucial parameter influencing the drug bioavailability, the availability of drugs in a correct concentration at the site action (Khadka et.al, 2014). However, amongst major problems arise during the development of new drugs in pharmaceutical industry nowadays is poor aqueous solubility. In recent years, poor water solubility number of drugs has increased for about 70% (Censi et al., 2015). This problem becomes the main reason why pharmaceutical compounds introduced into the market place are less than 1% (Abd Rahim et al., 2015). The drug substances are classified into four classes according to Biopharmaceutical Classification System (BCS), based on their aqueous solubility and intestinal permeability (Khadka et.al., 2014) .

Co- crystallization is one of the methods that can be used in order to improve the solubility and bioavailability of the drugs. Co- crystallization is defined as the alteration of molecular interactions and composition of pharmaceutical materials that comprised of active pharmaceutical ingredients (API) stoichiometric of an acceptable co- former. The co-crystal can be formed via several types of interaction which are hydrogen bonding, pi- stacking, and Van der Waals forces. The co- crystal former play an essential role in co- crystal formulation in helping the API to disintegrate into small particles, hence these particles able to be transported to the blood stream where the drug is intended to play its role and still protect the stability of the drugs to be at their greatest benefits and effectiveness (Abd Rahim et al., 2016). Carbamazepine is one of the examples of poor water soluble drug and used as a model drug by researchers in engaging the study of crystal engineering. According to BCS, carbamazepine is characterized as class II drug, in which this drug exhibit poor water solubility and high intestinal solubility. Acids and amides have been widely studied as co- formers in the co- crystallization of carbamazepine (CBZ) due to the hydrogen bonding sites availability of the CBZ drug molecule (Ziyaur Rahman et al., 2011). The CBZ- FUM co-crystal can be obtained due to the presence of amide group of the carbamazepine and carboxyl group of the carboxylic acid that is capable to form supramolecular heterosynthons. According to Abd Rahim et al., (2015), the co- crystal of CBZ- FUM has formed two polymorphic forms which are Form A and Form B polymorph. The polymorphic forms of this co- crystal possess different solubility and dissolution due to difference in the molecules packing in the crystal lattice. The polymorphs forms can be produced using different methods of crystallizations, and with various mole ratio between CBZ and fumaric acid. The solution condition such as the presence of solvents also has significant influence on polymorphic crystallization as the solvents effect nucleation and crystal growth (Abd Rahim et al., 2015).

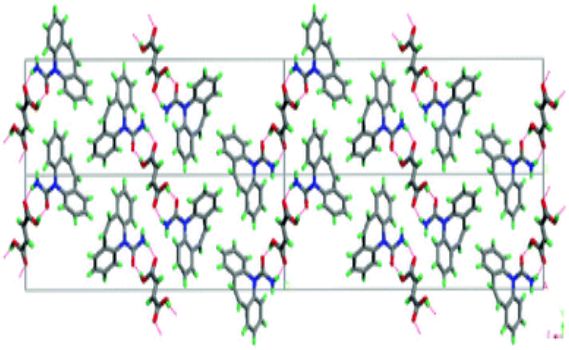


Figure 1.1: Supramolecular heterosynthons between carboxylic acid and amide group. Dashed lines (pink) represent the hydrogen bonds (Abd Rahim et al., 2013)

The crystal growth and dissolution was affected by its adsorption and incorporation from solution into its surface (Zhang et al., 2008). Molecular dynamic (MD) simulation plays a crucial role in drug design and structural optimization in drug discovery (Gao et al., 2003). It is an excellent tool in characterizing the involved interactions at the molecular level that give the limitation on the solubility or dissolution of drug compounds in a particular solvent that are not possible to investigate experimentally (Piana et al., 2005). The first molecular dynamics (MD) simulation of a drug crystal dissolving has reported by Gao et al., (2013) to gain molecular level understanding on dissolution of drug in aqueous media. The simulation was performed by dissolving acetaminophen crystal Form I in aqueous sodium chloride (NaCl) solution at 37ºC for 10 ns. This simulation showed interesting details on how dissolution process occurs. Based on this simulation, it shows that the dissolution of molecules process occurs first on the molecules located on the corners and then followed by those located on (1 0 0), (0 1 0), and (0 0 1) surfaces with slight variation. To explain the mechanism of this phenomena, a new sites for the next wave of molecules to dissolve is created once a molecule breaks free from the corners or edges instantaneously and this such dynamic dissolution process will be continues until the whole crystal disappear or until saturation is achieved. Thus this dissolution simulation results are relevant in the context of particle size reduction to enhance dissolution of poor water- soluble compounds. However, the dissolution of CBZ- FA Form B with the influence of ethanol solvent has not been studied. Therefore, this study is aimed to predict the dissolution of carbamazepine- fumaric acid (CBZ- FUM) form B polymorph in ethanoic solution using molecular modelling approach to establish the interaction of ethanol molecule with co- crystal carbamazepine- fumaric acid (CBZ- FUM).

2. METHODOLOGY

2.1. Materials

The initial structure of CBZ- FA co- crystal in its crystal lattice was obtained from Cambridge Structural Database (CSD). CBZ- FA crystallizes in a monoclinic lattice with space group P21, Z= 4, and cell parameters a= 5.0356 Å, b= 9.3352 Å, c= 31.2222 Å, and β= 93.442º. CBZ- FUM is packed in 4 asymmetric units in the unit cell, with a pair of molecule CBZ- FUM in an asymmetric unit.

2.2. Computational Methods

The computational program package, Material Studio 4.4, from ACCELRYS was used to carry out the modelling of crystal growth morphology involving the calculation in determining of atomic charges and lattice energy and morphology prediction .Then MD simulation to predict the dissolution behavior of CBZ- FUM co- crystal with ethanol solvent was carried out. The interfacial model was employed to investigate dissolution behavior of CBZ- FUM with ethanol as solvent.

2.2.1 Atomic Charges Determination

The calculation of atomic charges was calculated by using two methods: the MNDO method in MOPAC and an ab initio DMol3 density functional theory (DFT) of the quantum mechanical code in Material Studio. DFT quantum code in Material Studio is an initio method that can be used to estimate the electronic properties of atoms accurately. The MNDO calculation in MOPAC was performed using a single- consistent-field method, meanwhile the other two charges types which are Mulliken and Hirsfeld were calculated in Material Studio by using DFT quantum mechanical code with PW91 gradient corrected functional correlation, an "all electrons" core treatment, and the DNP basis set.

2.2.2 Lattice energy Determination and Morphology Prediction

In Material Studio, the potential functions used were Compass, Dreiding, Universal, CVFF and PCFF. The prediction of CBZ-FUM morphology via the calculation of lattice energy using the MS program package was as follows. Firstly, the CBZ- FUM was obtained from CSD. The atomic charges of the CBZ- FUM molecules were determined by using the force fields assigned to the optimization process. The structure was subjected to geometry optimization and then energy minimization, also by using the potential function mentioned earlier. The co- crystal morphology was predicted by applying an energy attachment (EA) method, which is an embedded module available in the MS software. The same potential function was used (as the optimization and energy minimization process) for the morphology prediction procedure. For validation of the predicted model, the lattice energy obtained from simulation and experimental lattice energy was carried out. The experimental lattice energy was carried out using the equation below:

$$E_{latt} = -\Delta H_{sub} - 2\,RT \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where E_{latt} is the lattice energy, ΔH_{sub} is the enthalpy of sublimation, R is the gas constant, and T is the temperature. In this work, the experimental heat sublimation, H_{sub}(Equation 1) for the CBZ- FUM was not available, and thus the value was calculated using equation 2:

$$\Delta H_{sub}(298.15\ K) \approx \Delta H_{sub}(T_{fus}) + \{[\,C_{p,m}(cr)_{estd} - C_{p,m}(l)_{estd}]\,(298.15 - T_{fus})\} \ldots\ldots (2)$$

where the $\Delta H_{sub}(T_{fus})$ value is determined by DSC at the melting point temperature (Chickos et al.,2002) and $C_{p,m}(cr)_{estd}$ and $C_{p,m}(l)_{estd}$ (expressed in J/mol. K) represent the estimated isobaric molar heat

capacities of crystal (cr) and liquid (l) at 298.15 K using a group additivity approach proposed by Chickos et al., (2002).

2.2.3 Prediction Dissolution of CBZ- FUM Co-Crystal in Ethanolic Solvent

The dissolution of CBZ- FA co- crystal with ethanol was also simulated using Material Studio. A solvent layer was filled with distributed ethanol molecules is built with the layer density set to be 0.789 g/cm^3 by the Amorphous Cell tool. Geometry optimization, followed by MD simulations (5 ps with time step 0.1 fs at temperatures of 571 ºC and 788 ºC, using the Berendsen thermostat) for the layer of solvent was carried out to make ethanol molecules uniformly distributed in the layer of solvent. The ethanol solvent consisted of 17 100 molecules. The crystal consists of 2 508 molecules was then placed in an ethanol slab. The resulting structure, containing a total of 19 644 molecules, was then subject to geometry optimization in subsequent simulations. Prior the simulations was run, the molecules of the co- crystal at the center was constrained and only 2 layers of molecules was left to unconstrained. The molecules of co- crystal at the center were constrained as this study is aimed to demonstrate the dissolution of CBZ- FUM co- crystal at the edge corners and surfaces of the co- crystal. For the purpose of studying the dissolution and solubility of CBZ- FUM co- crystal, a layer for molecules of ethanol molecules, the calculation of self- diffusion coefficient using means square displacement (MSD) in the solvent is executed to disclose the dynamics of the crystals. The MD simulations were carried out at 571 ºC and 788 ºC in the NVT ensemble.

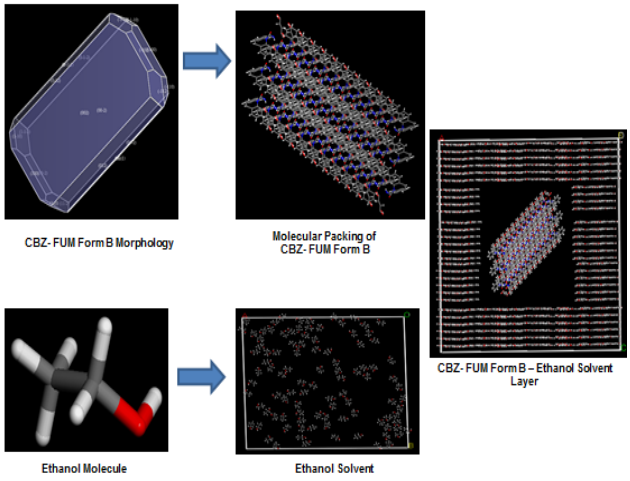


Figure 2.1: The layer that consists of CBZ- FUM Form B co- crystal molecular packing with ethanol solvent

3. RESULTS AND DISCUSSION

3.1 Atomic Charges Determination

DFT calculation performed with PW91 functional was chosen as thw most accurate ab initio screening method of carbamazepine- fumaric acid (CBZ- FA) co- crystal formation through lattice energy calculation (verified by comparison using % error between experimental lattice energy and simulated lattice energy values). Chan et al., (2013) reported that DFT calculation with the PW91 function is an accurate thermodynamic approach that can predict reliably the stability of the co-crystals relative to their solid- state co- formers.

3.2 Lattice energy Determination and Morphology Prediction

The predicted lattice energy in Table 1, it is clearly shows that the values of lattice energy values are very dependent on the charges sets and potential functions used. Different type of charges and potential functions exhibit different values for morphology lattice energies.

Table 3.1: Lattice energies (kcal/mol) of CBZ- FA using different charges set and potential functions

Potential function	Charge type	E_{latt} (kcal/ mol)	Percentage error (%)
Compass	MNDO	-48.696	3.066
	Mulliken	-72.781	44.878
	Hirsfeld	-27.092	46.071
Dreiding	MNDO	-37.902	24.55
	Mulliken	-159.435	217.372
	Hirsfeld	-50.310	0.1473
Universal	MNDO	-38.441	23.48
	Mulliken	-50.342	0.2110
	Hirsfeld	-31.7055	36.887
CVFF	MNDO	-62.366	24.15
	Mulliken	-27.970	44.323
	Hirsfeld	-28.552	0.4316
PCFF	MNDO	-50.237	0.0020
	Mulliken	-16.838	66.482
	Hirsfeld	-23.065	54.087
E_{latt} (calculated)	-50.236		

The calculated lattice energy used in this work was - 50.236 kcal/mol. The lattice energy obtained from the simulation by Material Studio was compared with the lattice energy determined using the summation of intermolecular interaction method by using equation 1. Based on the lattice energy calculated by using Material Studio and MOPAC/MNDO, the values of lattice energy obtained were at the range of -159.435 kcal /mol to -16.838 kcal /mol. The lattice energy calculated by using MOPAC/ MNDO charge and PCFF force field exhibits the lowest lattice energy value difference when compared to the experimental lattice energy that was calculated by using Equation 1 with percentage error of 0.0020%. According to Anuar et al., (2012), lattice energy using potential charge and potential function is considered to be most compatible to be used to predict the morphology when the percentage error less than 5% when compared with experimental value. However, for dynamic simulation purposes of carbamazepine- fumaric acid co- crystal, the lattice energy calculated by using Hirsfeld charge with PCFF force field was chosen. This selection was based on similarity of morphology between the experimental morphology.

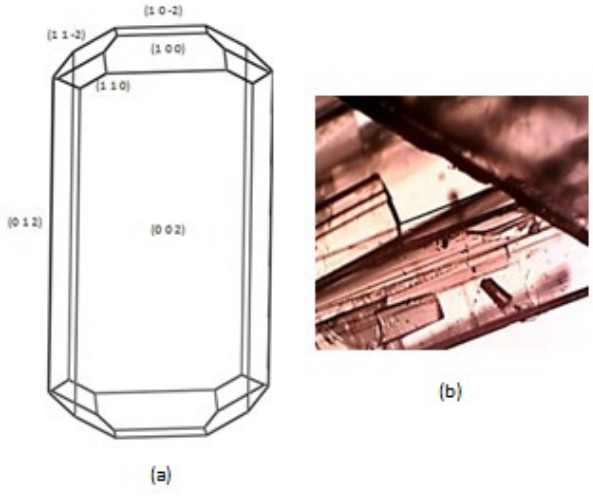


Figure 3.1: The morphology of CBZ- FA Form B co- crystal (a) obtained from simulation using MS software (b) obtained from experiment (Abd Rahim et al., 2015)

The morphology obtained from the molecular modelling by using MS software is shown in Figure 3.2(a). The morphology of CBZ-FA obtained from the molecular modelling was then compared with the experimental morphology from paper Abd Rahim et al., (2015) as shown in Figure 3.1(b). The morphology from molecular modelling using MS software shows a good agreement when compared to the experimental morphology. According to Abd Rahim et al., (2015), CBZ- FA co-crystal has needle- like morphology as shown in Figure 3.1 (b). The co-crystal with this needle- like morphology was grown in an ethanolic solvent whilst the predicted morphology was packed in vacuum condition, thus this result in the difference of the morphology. According to Anuar et al., (2012), the presence of additive molecules is known to alter the morphology of the crystal. From the predicted morphology obtained from simulation in Figure 1(b), the morphology shows an elongated hexagonal shape of CBZ- FA co- crystal that was bounded by dominant (0 0 2), (0 0 -2), (0 1 2), (0 -1 2) facets elongated along y- axis, facets (1 0 0), (1 0 -2), (-1 0 0) and (-1 0 2) at the top and bottom of morphology with the long and thin (0 -1 1) and (0 1 1) facets, the angled facets (1 1 0), (1 -1 0), (-1 1 2) and (-1 -1 2). The long and thin facets (0 -1 1) and (0 1 1) are not clearly visible.

Table 3.2: Important intermolecular bonds (calculated using Material Studio) for CBZ- FA co- crystal (in kcal/ mol)

Face	Multiplicity	d_{hkl}	Eatt vdW	Eatt Electrostatic	Eatt Total
(0 0 2)	2	15.58	-3.77	-6.72	-10.49
(0 1 2)	4	8.01	-13.74	-10.51	-24.24
(1 0 0)	2	5.03	-37.98	-8.98	-46.96
(1 0 -2)	2	4.87	-35.89	-10.97	-46.87
(1 1 0)	4	4.43	-43.43	-5.18	-48.61
(1 1 -2)	4	4.32	-42.32	-11.34	-53.65

Table 3.2 shows the breakdown of attachment energy calculated, with the attachment energy contributions from van der Waals (vdW) and electrostatic interactions, at the important facets of the CBZ-FUM Form B crystal. The dominating (0 0 2) facet is with the lowest total attachment energy of -10.49 kcal/ mol and the slowest growing face which indicate the most stable surface while facet (1 1 -2) is with the highest total attachment energy of -53.65 kcal/mol. The slowest growing face is the most stable face, hence more difficult to dissolve in solvent (Hammond et al., 2005). The molecular packings and orientations for each facet are different as illustrated in Figure 2. Facet (1 0 0) and (1 0 -2) are with the highest attachment energies and the fastest growing facets built by the hydrophobic region of the molecular structure, in which only the weak van der Waals interaction dominates these facets(Anuar eta al.,2012). For facets (0 0 2), (0 1 2), (1 1 0) and (1 1 -2), the hydrogen bond interactions can be clearly observed from the crystal surface. The electrostatic energy for all these facets was contributed by the presence of oxygen atoms which are known to have high polarity on the terminating of these facets. The facets (0 1 2) and (1 0 -2) are with the highest electrostatic energy of -10.51 kcal/ mol and -10.97 kcal/ mol respectively. The presence of nitro groups exposed to these facets which are also known to have high polarity contribute to the high electrostatic energy for these faces.

3.3 Prediction Dissolution of CBZ- FUM Co- crystal in Ethanolic Solvent

The dissolution behaviour of the CBZ- FUM co- crystal was simulated using molecular dynamic (MD) and the result demonstrated the crystal molecules being separated from the crystal surface entering the solvent phase. According to Gao et al.,(2013), dissolution involves the breaking of intermolecular interactions that held the neighbouring molecules on a solid either crystalline or amorphous to make them closely associated with each other. Then, these molecules will be form new interactions with dissolution medium. Goa et al., (2013) also stated that the crystal molecules leave the crystal surfaces in an organized manner. The crystal molecules located at corners leave the crystal surface into solvent phase first, followed by those located on edges and finally the flat faces of crystal. Figure 3.3 shows an illustration on the position of CBZ- FUM facets. The angled facets of (1 1 -2) is predicted to dissolve first as these facets located at corners, followed by facets (1 0 -2), and facet (0 1 2) will be dissolved last.

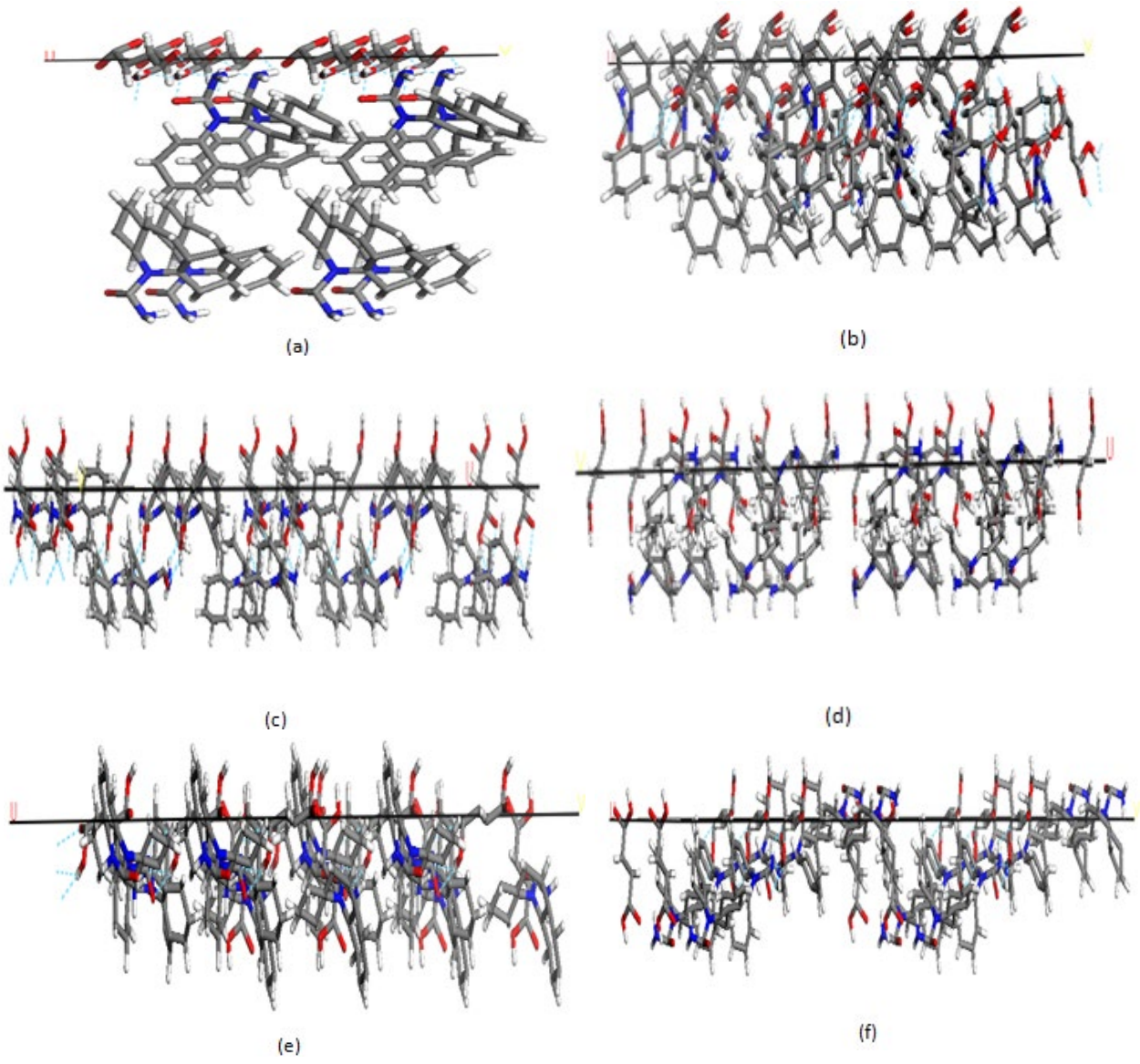


Figure 3.2: Molecular packing diagram of CBZ- FUM illustrating the surface chemistry of crystal facets: (a) (0 0 2), (b) (0 1 2), (c) (1 0 0), (d) (1 0 -2), (e) (1 1 0), (f) (1 1 -2) determined using the Material Studio, the force field utilized was PCFF. Colour: Red, blue, white and grey indicate oxygen, nitrogen, hydrogen and carbon atom, respectively and the solid line represent the crystal face. Blue dashed lines represent the hydrogen bonding.

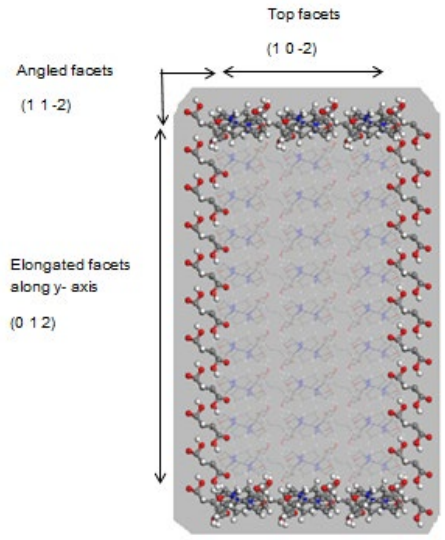


Figure 3.3: Illustration of the CBZ- FUM facets

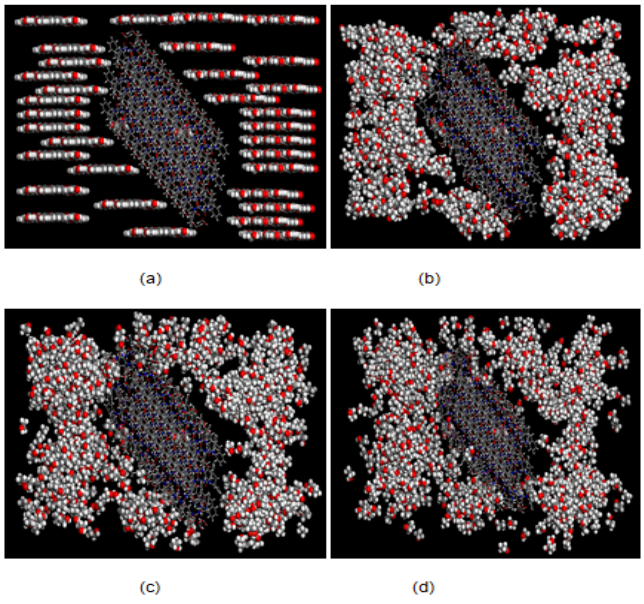


Figure 3.4 Demonstration of the molecules release profile with time. Undissolved CBZ- FUM co- crystals are shown in the line style, meanwhile dissolved CBZ- FUM co- crystal are shown in ball and stick diaplay style. (a) image taken at 0 ps (b) image taken at 1 ps (c) image taken at 3 ps (d) image taken at 5 ps temperature 788 ºC

The simulation on the dissolution of CBZ- FUM co-crystal in ethanol solvent system was simulated for 5 ps (500 frame). CBZ- FUM molecules gradually left the crystal and over time accumulated into the solvent phase. The dissolved molecules were seen to move around within the ethanol slab in a random manner and sometimes repositioned itself close to the surfaces of the co- crystal. Figure 3.4 showed the snapshots of the dissolution behaviour of the CBZ- FUM co- crystal in ethanol solvent system at time 0 ps, 1 ps(100 frame), 3 ps(300 frame) and 5 ps(500 frame) respectively. From Figure 3.4, it can be observed obviously that the crystal became smaller, indicates the increasing numbers of the crystal dissolved into the solvent phase. This figure also clearly shows that the dissolution only occurs for molecules located on the surface layer of crystal meanwhile the crystallinity (long range- order) in the center of the crystal is preserved. This result is consistent with findings by Gao et al.,(2013).

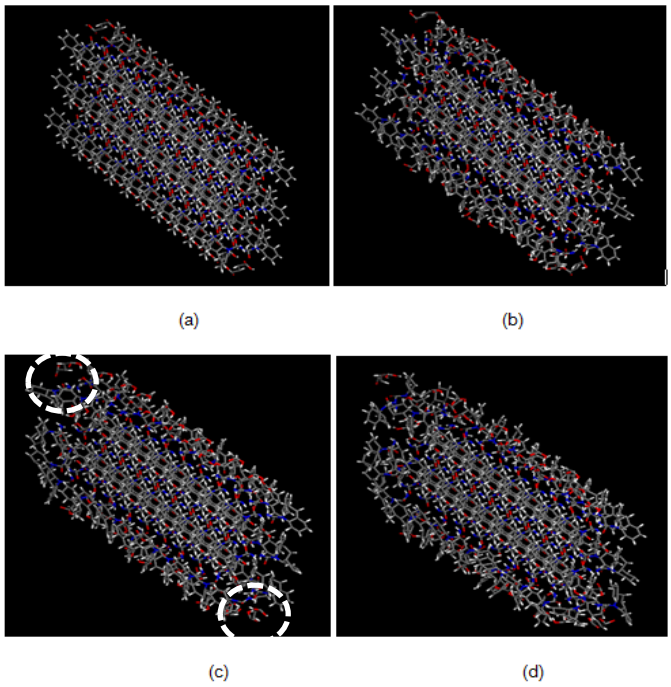


Figure 3.5: (a) The CBZ- FUM Form B co- crystal after equilibration (at 0 ps) (b) image taken at 1 ps (c) image taken at 3 ps (d) image taken at 5 ps at temperature 788 ºC. Circles drawn highlight the dissolution of CBZ- FUM Form B in ethanol solvent

The co- crystal of CBZ- FUM in the ethanol slab was equilibrated to reach lower energy. Figure 3.5 (a) is the snapshot of the co- crystal at the end of equilibration, which exhibits some interesting features. First, it can be seen that the co- crystal remained attached to each other, contributing to the overall three- dimensional long- range order as originally built. Then, each molecules of co- crystal CBZ- FUM moved around within limited boundaries which represent the vibrational and rotational movement of molecules in the crystal lattice. This illustration shows that the molecules located on outer layer appeared to be much more mobile compared to those located deeper inside the crystal. This figure also shows the fact that crystal molecules located at the corners dissolved first. The crystal molecules located at corners started to leave the crystal surfaces at time 3ps (in circle) as shown in Figure 3.5(c). This means that angled facets of (1 1 -2) dissolved first.

3.4 Interaction of CBZ- FUM with Solvent

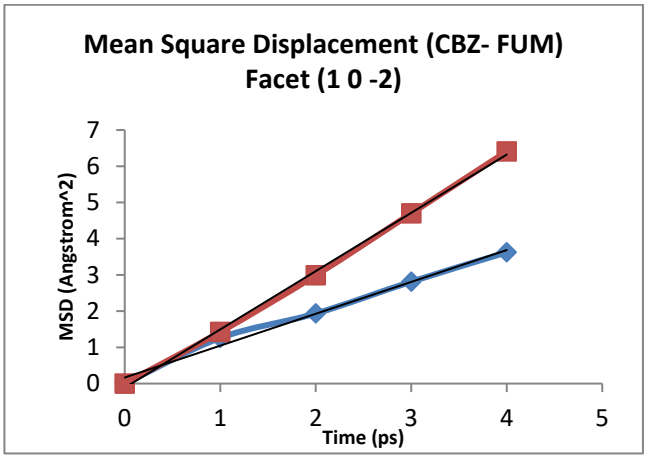
The dynamics of the dissolution of CBZ- FUM in ethanolic solvent can be examined by the mean square displacement (MSD) measurement of ethanol molecules and CBZ- FUM molcules.The MSD values that can be calculated by using equation (3) as shown below:

$$MSD = \sum_{i-1}^{N} \langle |r_i(t) - r_i(0)|^2 \rangle \text{ ..... (3)}$$

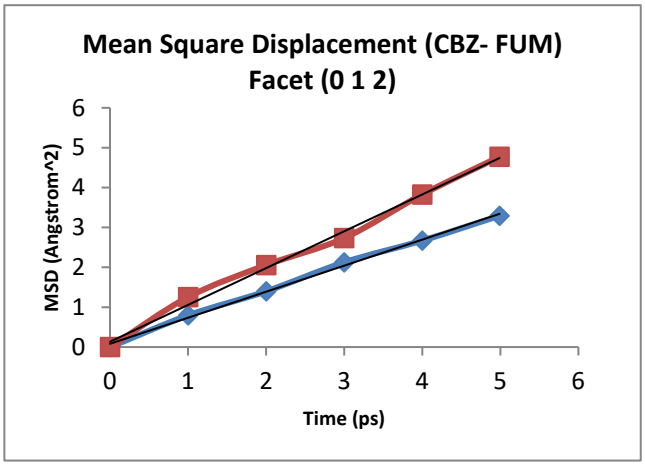
where N is the number of molecules and $r_i(t)$ is the position of molecules i at time t. The MSD represents the motion of molecules with respect to their original position, and the value is related to the diffusion coefficient (D) as shown in equation 4 as below:

$$D = \frac{1}{6}\lim_{t\to\infty}\frac{d}{dt}\sum_{i-1}^{N}\langle|r_i(t) - r_i(0)|^2\rangle \quad \ldots\ldots (4)$$

Molecules in liquids and gases do not stay in place, but move about constantly. The molecules of a simulation system move all the time and their positions are difference at the different moment. The longer displacement increment indicates the stronger activity. Mean Square Displacement (MSD) is a measure of the average distance of a molecules travel and implying the mobility of the atoms by calculating self-diffusion coefficient, D. Hence, the diffusion coefficient (D) can be used to measure the solubility of the of the crystal molecules in the solvent (Gao et al., 2013).



(a)



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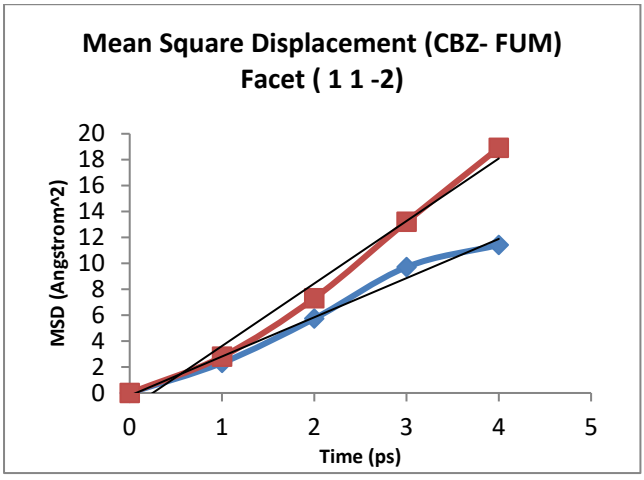

(c)

Figure 3.6 Mean Square Displacement (MSD) of different facets and temperatures of the CBZ- FUM in ethanol solvent (a) facet (1 0 -2) (b) facet (0 1 2) (c) facet (1 1- 2) at temperatures 571 ºC and 788 ºC. Red line represent temperature 788 ºC and blue line represent temperature 571 ºC.

For this study, MSD analysis was made at two different temperatures which are at temperature 571 ºC and 788 ºC. Figure 3.6 shows the MSD curves of the CBZ- FUM in ethanol solvent at different temperatures. Based on the MSD curves shown, it is obvious that the mobility of CBZ- FUM molecules becomes greater with increased temperatures which indicate that solubility becomes much easier at higher temperature. This phenomenon can be related to the higher energy of molecules due to high temperature. According to this figure, it is also shows that the CBZ- FUM at facet (1 1 -2) located at the corner edges has higher mobility at temperature 571 ºC compared to the other facets. This is because these two facets have the high attachment energy compared to other facets. The highest attachment energy leads to the fastest growth of the co- crystal and the smallest facets and hence with the highest surface energy calculated by using equation 5. Thus, these facets tend to dissolve easier in the solvent. The same results were also observed for temperature 788ºC. The diffusion coefficient (D) obtained from their MSDs, listed in Table 3.3, also support the above statement. The diffusion coefficient (D) at facet (1 1 -2) are highest, followed by facet (1 0 -2) and finally facet (0 1 2) for both temperatures. This means the dissolution at facet (1 1 -2) is higher compared to other facets.

$$\gamma_{hkl} = \frac{ZE_{att}\,d_{hkl}}{2V_{Cell}N_A} \quad \ldots\ldots (5)$$

where Z represent the amount of molecules in the unit cell of volume V_{cell}, E_{att} represent the attachment energy, d_{hkl} represent the d spacing and N_A is Avogadro's constant.

Table 3.3: Diffusion coefficient (D) and surface energy calculated for the molecules of CBZ- FUM in ethanol solvent for different facets and temperature

Facet	Diffusion Coefficient (D) (10^{-8} cm^2/s)		Surface energy
	T-571 ºC	T-788 ºC	
(1 1 -2)	1.928	4.370	$-5.250\ x10^{-25}$
(1 0 -2)	1.115	1.882	$-5.174\ x10^{-25}$
(0 1 2)	0.548	0.795	$-4.402x10^{-25}$

4. CONCLUSION

The results of lattice energy and morphology prediction as well as molecular dynamic (MD) simulation of CBZ- FUM Form B polymorph dissolving into ethanolic solvent have presented here. The prediction of lattice energy has successfully carried out, in which the comparison of percentage error is within 0.002% with the predicted morphology (in vacuum) is in elongated hexagonal shape. In this work, the simulation of dissolution of CBZ- FUM (Form B) has been successfully simulated. The results showing the dissolution is preferred to occur at the corner edges of the crystal and in agreement with work done by Gao et al., (2013).The results are also supported by diffusion coefficient and surface energy results calculated. These results also can be related with the fundamentals of particle size reduction in enhancing dissolution rate. The small size of the molecules located at the edge corners made them more tend to dissolve faster compared to those molecules located at the surfaces. The results presented from this work clearly show the reduction of particle sizes can enhance the dissolution rate of poorly soluble drugs.

Acknowledgements

The authors would like to thank the Faculty of Chemical Engineering, UiTM for the facilities support given for this work. This work is part of grant 600-IRMI/MyRA 5/3/BESTARI/023/2017. This final year project was prepared as a fulfillment for the Degree of Bachelor of Chemical Engineering and Bioprocess.

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